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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/731,941		James M. Allen	226272001403	6840

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Catherine M. Polizzi
Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, CA 94304-1018

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/731,941	ALLEN, JAMES M.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Non-Final Rejection

Priority

Cross Reference to related application listed in paper 5a filed on 10/29/01 is acknowledged.

The cancellation of claims 18-20, the addition of claim 22, and the amendment to claims 1, 3, 6-12, 15-17, and 21 is acknowledged in paper no. 5a filed in 10/29/01.

Information Disclosure Statement

The information disclosure statement filed on September 20, 2001 does not fully comply with the requirements of 37 CFR 1.98 because: applicant does not properly the date a WIPO document (no. 15) listed on the 1449. The date should read 12/8/1994. In addition, only the abstract of German Patent 4436664 will be considered. Furthermore, only claims 1 and 6 of AU document 6789867 and claims 1, 7, and 13 of AU document 688428 will be considered.

The journal articles (39-41 and 43-45) listed on the 9/20/01 IDS that were filed with application 08/564,167 have been inadvertently lost. Any publications not initialed have not been considered. Applicants may file copies of these references when filing the new IDS.

References (except for journal articles 39-41 and 43-45) have been considered by the examiner, but in order to have the WIPO document initialed and dated on the 1449, a new 1449 properly citing the document must be filed with the response to this office action. Failure to comply with this notice will result in the above mentioned information disclosure statement being placed in the application file with the non-complying information not being considered. See 37 CFR 1.97(i).

Claims 1-17 and 21-22 are pending examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-5 and 10-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 10 are vague and indefinite for the phrase "mammalian cell, which comprises a stably **integrated** AAV cap gene operably linked to a promoter, and a stably **integrated** AAV rep gene operably linked to a helper virus-inducible heterologous promoter, wherein p5 promoter function has been replaced by the helper virus-inducible heterologous promoter" because the claims do not define whether the p5 promoter in the genome of the cell was modified before it was in the cell or that the p5 promoter function will be replaced by adding a plasmid with an AAV rep gene operably linked to a helper virus-inducible heterologous promoter. Clarification is requested.

Claims 4 and 13 are vague and indefinite because neither claim further limits the claim it was dependent on. Both claims state the phrase "the combined rep and cap genes of AAV in which the p5 promoter has been replaced by a heterologous promoter" and the structural limitation already appears in the independent claims. If the applicant is trying to claim that the rep and cap gene are under control of the same heterologous promoter, then applicant should amend the claims to read on that particularly intended limitation.

The statement in claims 2-5, "**A** method according to claim 1" is indefinite because it does not point out which method "**A** method" is referring to in the claim. The dependent claim should state "**The** method according to claim 1."

The statement in claims 11-17, "**An** AAV packaging cell of claim .." is indefinite because it does not point out which packaging cell, "**An** packaging cell" is referring to in the claim. The dependent claim should state "**The** AAV packaging cell of claim..."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-4, 6-8, 10-13, 15-17, and 21-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Flotte et al. (US Patent No. 5,658,776, effective filing date 11/3/94). Flotte teaches a stable cell line containing an AAV CFTR vector and a pSVneo plasmid (columns 18-19, Examples 8). The pSVneo plasmid contains a heterologous promoter (HIV-LTR) operably linked to the rep and cap gene of AAV (Figure 2). In addition, Flotte teaches that the

heterologous promoter can be a metallothionein promoter; a steroid hormone inducible promoter, promoters which would be inducible by the helper virus such as adenovirus early gene promoter inducible by adenovirus E1A protein, or the adenovirus major late promoter; herpesvirus promoter inducible by herpes virus proteins or vaccina or poxvirus inducible promoters (columns 12 and 13). Flotte further teaches a method of determining the titer of an AAV vector stock and shows that the titer represented a several-fold improvement over another AAV stock with a known titer (columns 15 and 16, Example 4, columns 16, line 15- column 17, line 12, Example 7).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

Claims 1-17 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (IDS, Journal of Virology, 1994) taken with Johnson (US Patent 5,568,785, effective filing date 6/6/94). Yang teaches the generating of inducible Rep-expressing cell lines

comprising the rep gene under control of the mouse metallothionein I promoter (mMT-I). Yang reports that their cell lines are capable of assembling infectious viruses containing a mutant rep gene or a vector comprising of a heterologous gene (abstract and materials and methods, page 4847-4849). Yang further teaches using the adenovirus type 2 (helper virus) for co-infection (page 4848). However, Yang does not teach a rep-expressing cell lines also comprising a stably integrated cap gene, rather Yang teaches providing the cell lines are capable of *trans* activating the cap gene promoter (page 4854).

However, at the time the invention was made, Johnson teaches packaging cell lines, which comprises stably integrated rep-cap sequences (columns 9 and 10, Example 5). Johnson further teaches that these cell lines are useful for in a method for packaging rAAV (columns 8-9, Example 4 and column 10, Example 6). In addition, Johnson reports that these stably transfected cell lines arise from the need for more efficient methods for packaging rAAV genomes, thereby eliminating unnecessary transfection events genomes (columns 2 and 3). Furthermore, Johnson teaches a method of determining the titer of rAAV compared to a known titer of AAV (column 9, lines 13-16).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Yang taken with Johnson, namely to produce a rep-cap expressing cell for use in a method of packaging rAAV vector with a reasonable expectation of producing stable cell lines comprising both inducible rep and cap sequences. One of ordinary skill in the art would have been motivated to include cap in a rep-expressing cell line, as it was art-recognized goal to provide more efficient methods of packaging rAAV by eliminating co-transfection steps. In addition, one of ordinary skill in the art would have

motivated to determine the titer of rAAV compared to a known titer of rAAV because of the routine practice of determining the titer of rAAV.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1-17 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flotte et al. (US Patent No. 5,658,776, effective filing date 11/3/94) taken with Trempe et al IDS, US Patent No. 5,837,484). Flotte teaches a stable cell line containing an AAV CFTR vector and a pSVneo plasmid (columns 18-19, Examples 8). The pSVneo plasmid contains a heterologous promoter (HIV-LTR) operably linked to the rep and cap gene of AAV (Figure 2). In addition, Flotte teaches that the heterologous promoter can be a metallothionein promoter; a steroid hormone inducible promoter, promoters which would be inducible by the helper virus such as adenovirus early gene promoter inducible by adenovirus E1A protein, or the adenovirus major late promoter; herpesvirus promoter inducible by herpes virus proteins or vaccina or poxvirus inducible promoters (columns 12 and 13). Flotte further teaches a method of determining the titer of an AAV vector stock and shows that the titer represented a several-fold improvement over another AAV stock with a known titer (columns 15 and 16, Example 4, columns 16, line 15- column 17, line 12, Example 7). However, Flotte does not specifically teach using the heterologous promoter, mMT-1.

However, at the time the invention was made, Trempe teaches a stable mammalian cell line with a rAAV rep gene operably linked to a heterologous promoter, which cell line contains a gene encoding functional Rep protein (column 14, claim 1). Trempe further teaches that the heterologous promoter is an mMT-1 (column 14, claim 3). In addition, Trempe teaches that the

cell line is infected with a helper virus such as adenovirus or herpes virus and a vector, wherein the vector can comprise of an AAV cap gene (column 7, lines 3-15). The cap gene may be expressed from either a homologous AAV promoter or from a heterologous promoter (column 7, lines 8-15).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made as routine practice to combine the teaching of Flotte taken with Trempe to specifically use the mMT-1 promoter because of the usage of that specific promoter in producing a construct (heterologous promoter operably linked to an AAV rep gene) used for producing a cell line for packaging rAAV. One of ordinary skill in the art would have been motivated to use the specific metallothionein I promoter because that specific promoter was well known in the art for use in producing a construct, which is used in producing a cell line for packaging rAAV.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
February 11, 2002

DAVE T. NGUYEN
PRIMARY EXAMINER